PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 October 2000 (09.10.00)	
International application No. PCT/US00/01086	**Applicant's or agent's file reference** PF-0659 PCT
International filing date (day/month/year) 14 January 2000 (14.01.00)	**Priority date** (day/month/year) 15 January 1999 (15.01.99)
Applicant HILLMAN, Jennifer, L. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 July 2000 (27.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christelle Croci
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 5/10, C07K 14/47, C12N 15/10, 15/63, C07K 16/18, A01K 67/027, G01N 33/48

A2

(11) Internati nal Publication Number: WO 00/42172

(43) Internati nal Publication Date: 20 July 2000 (20.07.00)

(21) International Application Number: PCT/US00/01086

(22) International Filing Date: 14 January 2000 (14.01.00)

(30) Priority Data:
60/183,019 15 January 1999 (15.01.99) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/183,019 (CIP)
Filed on 15 January 1999 (15.01.99)

(71) Applicant *(for all designated States except US)*: INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). TANG, Y., Tom [CH/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). LU, Dyung, Aina, M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US).

(74) Agents: HAMLET–COX, Diana et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PROTEINS ASSOCIATED WITH CIRCADIAN RHYTHMS

(57) Abstract

The invention provides human proteins associated with circadian rhythms (CIRYP) and polynucleotides which identify and encode CIRYP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of CIRYP.

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INTERNATIONAL SEARCH REPORT

Intern ...al Application No
PCT/US 00/01086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/10 C07K14/47 C12N15/10 C12N15/63 C07K16/18
A01K67/027 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIEBMANN P.M. ET AL.: "Circadian rhythm of the soluble p75 tumor necrosis factor (sTNF-R75) receptor in humans-a possible explanation for the circadian kinetics of TNF-alpha effects" INTERNATIONAL IMMUNOLOGY, vol. 10, no. 9, September 1998 (1998-09), pages 1393-1396, XP000864584 the whole document ---	1-17,20, 23
P,X	WO 99 40189 A (GENSET) 12 August 1999 (1999-08-12) SEQ ID NO:1 and 2 claims 1,9,13-17 ---	1,3,8-15
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	06.09.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schönwasser, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ...al Application No
PCT/US 00/01086

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 47540 A (HUMAN GENOME SCIENCES INC) 23 September 1999 (1999-09-23) page 135 -page 136; claims 1,7-17 page 343	1,3,8-16

A	NCI-CGAP: "National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index http://www.ncbi.nlm.nih.gov/ncicgap; ow91d05.x1 Soares_fetal_liver_spleen_1NFLS_S1 Homo sapiens cDNA clone IMAGE:1654185 3'similar to TR:Q94915 Q94915 DREG-2 PROTEIN.;, mRNA sequence." EMBL DATABASE ENTRY AI022747; ACCESSION NO. AI022747,19 June 1998 (1998-06-19), XP002138116	1,3

A	VAN GELDER R.N. ET AL.: "Extent and character of circadian gene expression in Drosophila melanogaster: identification of twenty oscillating mRNAs in the fly head" CURRENT BIOLOGY, vol. 5, no. 12, 1 December 1995 (1995-12-01), pages 1424-1436, XP000864597 cited in the application the whole document	1-17,20, 23

A	C A SMITH ET AL: "A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 248, no. 248, 25 May 1990 (1990-05-25), pages 1019-1022, XP002107350 ISSN: 0036-8075	1-17,20, 23

A	NOPHAR Y ET AL: "SOLUBLE FORMS OF TUMOR NECROSIS FACTOR RECEPTORS (TNF-RS). THE CDNA FOR THE TYPE 1 TNF-R, CLONED USING AMINO ACID SEQUENCE DATA OF ITS SOLUBLE FORM, ENCODES BOTH THE CELL SURFACE AND A SOLUBLE FORM OF THE RECEPTOR" EMBO JOURNAL, vol. 9, no. 10, 1 October 1990 (1990-10-01), pages 3269-3278, XP002025930 ISSN: 0261-4189	1-17,20, 23

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/US 00/01086

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 18,19,21,22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-17,20,23 partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-17,20,23 (partially)

An isolated polypeptide comprising: a) an amino acid sequence of SEQ ID NO:1, b) a naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, c) a biologically active fragment of SEQ ID NO:1, or d) an immunogenic fragment of SEQ ID NO:1; an isolated polynucleotide encoding said polypeptide; a recombinant polynucleotide comprising a promoter sequence operably linked to said polynucleotide; a cell transformed with said recombinant polynucleotide; a transgenic organism comprising said polynucleotide; a method for producing above mentioned polypeptide; an isolated antibody which specifically binds to said polypeptide; an isolated polynucleotide comprising: a) a polynucleotide sequence of SEQ ID NO:3, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to SEQ ID NO:3, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complemetary to b); an isolated polynucleotide comprising at least 60 contiguous nucleotides of said polynucleotide; a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of above mentioned polynucleotide; a pharmaceutical composition comprising an effective amount of above mentioned polypetide; a method of treating a disease or condition comprising the administration of said pharmaceutical composition to a patient; methods for screening of a compound comprising inter alia exposing a sample comprising said polypeptide to a compound; a method for screening of a compound for effectiveness in altering expression of a target polynucleotide comprising inter alia exposing a sample comprising said target polynucleotide to a compound.

2. Claims: 1-17,20,23 (partially)

Invention II relates to subject-matter as defined above for "invention I", with the exception, that invention II refers to the polypeptide sequence SEQ ID NO:2 and the respective nucleotide sequence SEQ ID NO:4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 18,19,21,22

Claims 18 and 21 refer to a pharmaceutical composition comprising inter alia an agonist compound or an antagonist compound, respectively, whereby said agonist and antagonist compounds were identified in a certain screening method. Further claims 19 and 22 refer to methods of treating a disease or condition comprising the administration of said pharmaceutical compositions to a patient.
No true technical characterization of such agonist and antagonist compounds is given and no such agonist and antagonist compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague and their subject-matter is not sufficiently disclosed and supported. No search can be carried out for such purely speculative claims whose wording is a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/US 00/01086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9940189 A	12-08-1999	AU 1049199 A	07-06-1999
		AU 1503099 A	05-07-1999
		AU 2294499 A	23-08-1999
		EP 1029045 A	23-08-2000
		WO 9925825 A	27-05-1999
		WO 9931236 A	24-06-1999
WO 9947540 A	23-09-1999	AU 3451799 A	11-10-1999
		AU 3072799 A	11-10-1999
		WO 9947538 A	23-09-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PF-0659 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/01086	14/01/2000	15/01/1999
Applicant		
INCYTE PHARMACEUTICALS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readble form.

   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   ☐ the text is approved as submitted by the applicant.

   ☒ the text has been established by this Authority to read as follows:

   HUMAN HOMOLOGUES OF PROTEINS REGULATED BY CIRCADIAN RHYTHMS

5. With regard to the **abstract,**

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ because the applicant failed to suggest a figure.

   ☐ because this figure better characterizes the invention.

   ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/01086

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 18,19,21,22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-17,20,23 partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-17,20,23 (partially)

An isolated polypeptide comprising: a) an amino acid sequence of SEQ ID NO:1, b) a naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, c) a biologically active fragment of SEQ ID NO:1, or d) an immunogenic fragment of SEQ ID NO:1; an isolated polynucleotide encoding said polypeptide; a recombinant polynucleotide comprising a promoter sequence operably linked to said polynucleotide; a cell transformed with said recombinant polynucleotide; a transgenic organism comprising said polynucleotide; a method for producing above mentioned polypeptide; an isolated antibody which specifically binds to said polypeptide; an isolated polynucleotide comprising: a) a polynucleotide sequence of SEQ ID NO:3, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to SEQ ID NO:3, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complemetary to b); an isolated polynucleotide comprising at least 60 contiguous nucleotides of said polynucleotide; a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of above mentioned polynucleotide; a pharmaceutical composition comprising an effective amount of above mentioned polypetide; a method of treating a disease or condition comprising the administration of said pharmaceutical composition to a patient; methods for screening of a compound comprising inter alia exposing a sample comprising said polypeptide to a compound; a method for screening of a compound for effectiveness in altering expression of a target polynucleotide comprising inter alia exposing a sample comprising said target polynucleotide to a compound.

2. Claims: 1-17,20,23 (partially)

Invention II relates to subject-matter as defined above for "invention I", with the exception, that invention II refers to the polypeptide sequence SEQ ID NO:2 and the respective nucleotide sequence SEQ ID NO:4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 18,19,21,22

Claims 18 and 21 refer to a pharmaceutical composition comprising inter alia an agonist compound or an antagonist compound, respectively, whereby said agonist and antagonist compounds were identified in a certain screening method. Further claims 19 and 22 refer to methods of treating a disease or condition comprising the administration of said pharmaceutical compositions to a patient.
No true technical characterization of such agonist and antagonist compounds is given and no such agonist and antagonist compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague and their subject-matter is not sufficiently disclosed and supported. No search can be carried out for such purely speculative claims whose wording is a mere recitation of the result to be achieved.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/01086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/10 C07K14/47 C12N15/10 C12N15/63 C07K16/18
A01K67/027 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIEBMANN P.M. ET AL.: "Circadian rhythm of the soluble p75 tumor necrosis factor (sTNF-R75) receptor in humans-a possible explanation for the circadian kinetics of TNF-alpha effects" INTERNATIONAL IMMUNOLOGY, vol. 10, no. 9, September 1998 (1998-09), pages 1393-1396, XP000864584 the whole document ---	1-17,20, 23
P,X	WO 99 40189 A (GENSET) 12 August 1999 (1999-08-12) SEQ ID NO:1 and 2 claims 1,9,13-17 ---	1,3,8-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	06. 9. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schönwasser, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 47540 A (HUMAN GENOME SCIENCES INC) 23 September 1999 (1999-09-23) page 135 -page 136; claims 1,7-17 page 343	1,3,8-16

A	NCI-CGAP: "National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index http://www.ncbi.nlm.nih.gov/ncicgap; ow91d05.x1 Soares_fetal_liver_spleen_1NFLS_S1 Homo sapiens cDNA clone IMAGE:1654185 3'similar to TR:Q94915 Q94915 DREG-2 PROTEIN.;, mRNA sequence." EMBL DATABASE ENTRY AI022747; ACCESSION NO. AI022747,19 June 1998 (1998-06-19), XP002138116	1,3

A	VAN GELDER R.N. ET AL.: "Extent and character of circadian gene expression in Drosophila melanogaster: identification of twenty oscillating mRNAs in the fly head" CURRENT BIOLOGY, vol. 5, no. 12, 1 December 1995 (1995-12-01), pages 1424-1436, XP000864597 cited in the application the whole document	1-17,20, 23

A	C A SMITH ET AL: "A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 248, no. 248, 25 May 1990 (1990-05-25), pages 1019-1022, XP002107350 ISSN: 0036-8075	1-17,20, 23

A	NOPHAR Y ET AL: "SOLUBLE FORMS OF TUMOR NECROSIS FACTOR RECEPTORS (TNF-RS). THE CDNA FOR THE TYPE 1 TNF-R, CLONED USING AMINO ACID SEQUENCE DATA OF ITS SOLUBLE FORM, ENCODES BOTH THE CELL SURFACE AND A SOLUBLE FORM OF THE RECEPTOR" EMBO JOURNAL, vol. 9, no. 10, 1 October 1990 (1990-10-01), pages 3269-3278, XP002025930 ISSN: 0261-4189	1-17,20, 23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/01086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9940189 A	12-08-1999	AU 1049199 A	07-06-1999
		AU 1503099 A	05-07-1999
		AU 2294499 A	23-08-1999
		EP 1029045 A	23-08-2000
		WO 9925825 A	27-05-1999
		WO 9931236 A	24-06-1999
WO 9947540 A	23-09-1999	AU 3451799 A	11-10-1999
		AU 3072799 A	11-10-1999
		WO 9947538 A	23-09-1999

~~09/615~~ 5650

09/889236

ATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PF-0659 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/01086	International filing date *(day/month/year)* 14 JANUARY 2000	Priority date *(day/month/year)* 15 JANUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 5/10, 15/10, 15/63; C07K 14/47, 16/18 and US Cl.: 435/69.1		
Applicant INCYTE PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 JULY 2000	11 MAY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer S. DEVI, Ph.D. JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/01086

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-56 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 57-59 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-9 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-5 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages None

[X] the claims, Nos. None

[X] the drawings, sheets/~~fig~~ None

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/01086

IV. Lack f unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   [X] restricted the claims.

   [ ] paid additional fees.

   [ ] paid additional fees under protest.

   [ ] neither restricted nor paid additional fees.

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   [ ] complied with.

   [X] not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   [ ] all parts.

   [X] the parts relating to claims Nos. 1-7, 10, 11 and 15 (partly).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	7	YES
	Claims	1-6, 10, 11 and 15	NO
Inventive Step (IS)	Claims	None	YES
	Claims	1-7, 10, 11 and 15	NO
Industrial Applicability (IA)	Claims	1-7, 10, 11 and 15	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-6 and 15 lack novelty under PCT Article 33(2) as being anticipated by SMITHKLINE BEECHAM CORPORATION (WO 9806734 A1).

SMITHKLINE BEECHAM CORPORATION disclose a polypeptide comprising a biologically active fragment of an amino acid sequence of SEQ ID NO: 1, a recombinant polynucleotide encoding the same and a host cell transformed with the polynucleotide (see abstract). See also the enclosed sequence search report.

Claims 10 and 11 lack novelty under PCT Article 33(2) as being anticipated by Hudson, T. (GeneEmbl Database, Accession No. Go5853, 1995).

Hudson discloses a polynucleotide sequence comprising at least 60 contiguous nucleotides of a polynucleotide of SEQ ID NO: 3 or a polynucleotide sequence complementary to SEQ ID NO: 3. See the attached sequence search report.

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over SMITHKLINE BEECHAM CORPORATION (WO 9806734 A1).

Since the method of incorporating a recombinant polynucleotide and expressing it via a transgenic organism is well known in the art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to insert SMITHKLINE BEECHAM CORPORATION'S polynucleotide into a transgenic organism to produce the instant invention, with a reasonable expectation of success, for the expected benefit of optimal gene expression.

---------- NEW CITATIONS ----------
WO 98/06734 A1 (SMITHKLINE BEECHAM CORPORATION) 19 February 1998, see entire document.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

IV. LACK OF UNITY OF INVENTION:

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:
This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Group I, claims 1-7, 10, 11 and 15, drawn to an isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 1 or a biologically active or immunogenic fragment thereof, a polynucleotide encoding the same, a cell transformed with the polynucleotide and a transgenic organism comprising the polynucleotide
Group II, claim 8, a method of producing the polypeptide of SEQ ID NO: 1.
Group III, claim 12-14, drawn to a method for detecting a target polynucleotide in a sample.
Group IV, claim 16, drawn to a method of treating a disease comprising administering the polypeptide of SEQ ID NO: 1.
Group V, claims 17-19, drawn to an agonist of the polypeptide of SEQ ID NO: 1, a method for screening a compound for effectiveness as an agonist of the polypeptide of SEQ ID NO: 1 and a method of treating a disease by administering the agonist.
Group VI, claims 20-22, drawn to an antagonist of the polypeptide of SEQ ID NO: 1, a method for screening a compound for effectiveness as an antagonist of the polypeptide of SEQ ID NO: 1 and a method of treating a disease by administering the antagonist.
Group VII, claim 23, drawn to a method for screening a compound for effectiveness in altering expression of a target polynucleotide.
Group VIII, claim 9, drawn to an antibody specific to the polypeptide of SEQ ID NO: 1.
Group IX, claims 1-7, 10, 11 and 15, drawn to an isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 2 or a biologically active or immunogenic fragment thereof, a polynucleotide encoding the same, a cell transformed with the polynucleotide and a transgenic organism comprising the polynucleotide
Group X, claim 8, a method of producing the polypeptide of SEQ ID NO: 2.
Group XI, claim 12-14, drawn to a method for detecting a target polynucleotide in a sample.
Group XII, claim 16, drawn to a method of treating a disease comprising administering the polypeptide of SEQ ID NO: 2.
Group XIII, claims 17-19, drawn to an agonist of the polypeptide of SEQ ID NO: 2, a method for screening a compound for effectiveness as an agonist of the polypeptide of SEQ ID NO: 2 and a method of treating a disease by administering the agonist.
Group XIV, claims 20-22, drawn to an antagonist of the polypeptide of SEQ ID NO: 2, a method for screening a compound for effectiveness as an antagonist of the polypeptide of SEQ ID NO: 2 and a method of treating a disease by administering the antagonist.
Group XV, claim 23, drawn to a method for screening a compound for effectiveness in altering expression of a target polynucleotide.
Group XVI, claim 9, drawn to an antibody specific to the polypeptide of SEQ ID NO: 2.

The inventions as defined above are drawn to two distinct polypeptide sequences and the corresponding polynucleotide sequences and methods of making or using the same. The special technical feature of Invention I is the first isolated polypeptide product of SEQ ID NO: 1 or fragments thereof. Inventions II and III respectively are drawn to a process of making the polypeptide and the first method of use of the polynucleotide encoding the same. The special technical feature of Invention X is the second isolated polypeptide product of SEQ ID NO: 2 or fragments thereof. Inventions XI and XII respectively are drawn to a process of making the polypeptide and the first method of use of the polynucleotide encoding the same. Although the first product of the invention and method of making and using the product is a permitted combination under PCT Rule 13.2, in the instant case, the special technical feature is already disclosed in the art. For instance, Black *et al.* (WO9806734-A1) disclose a polypeptide comprising an immunogenic fragment of SEQ ID NO: 1. Therefore, the special technical feature is not a unifying feature. Inventions V, VI and VII are drawn to a third, fourth and fifth product and a method of making and/or using the same. The same holds good with regard to the second product, i.e., the polypeptide of SEQ ID NO: 2 or fragments thereof. Similarly, the special technical feature unifying inventions X, XI and XII is already disclosed in the prior art. For instance, Barnes *et al.* (WO9817823 A1) disclose a polypeptide comprising an immunogenic fragment of SEQ ID NO: 2. Inventions XIII, XIV and XVI are drawn to a sixth, seventh and eighth product and a method of making and/or using the same. Clearly, the special technical feature is not a unifying feature.

It is further noted that, technically, the absence of a special technical feature would permit the separation of the method of making the polypeptide and a method of using the polypeptide.

In defining each of the apparent unifying feature was set forth and it is clear that the unifying feature of each invention is different from each other.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Co.ıtinued):

Database GenEmbl on GenCore version 4.5, Accession number G05853, HUDSON T., 'Whitehead Institute/MIT Center for Genome Research; Physically Mapped ESTs', 1995.